DETAILED ACTION

This office action is in response to the reply filed 2/28/2011 wherein claims 1-37 and 39-46 have been cancelled and claims 38, 47, 49-53, 56, 30, 62-73 have been amended..

Currently claims 38 and 47-73 are being examined.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/28/2011 has been entered.

Maintained/Modified Rejections

2. Claims **38**, **47**, **48**, **50-52, 62, 63, 66** and **68-69** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47, 48, 50-52, 62-63 and 66 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below.

MPEP 2111.03: For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention.

For purposes of examination the claims will be interpreted as reciting "comprising" language.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of:

a.) a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof (reads on the salt of **clm 48**); and

b.) ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present **claims 47** and **63**: See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present **claims 46** and **52**).

The Baker reference also teaches various dosage formulations such as the ones listed on column 4 (e.g. Examples 1-4), which tablet formulation "consists" of an oxycodone salt, Ibuprofen, and "at least one pharmaceutically acceptable excipient" including "microcrystalline cellulose", "starch", and "stearic acid". These formulations read on the oral dosage form of the instant **claim 38** except Ibuprofen is included instead of nabumetone. As recited in the various

Examples (col.4), the amount of Ibuprofen (a NSAID compound) ranges from 60-300 mg, which range reads on the range recited in **claim 51, 68-69**. For example daily dosages range from 10-120 mg/kg of ibuprofen (Col. 3, lines 55-56), which reads on instant claim **68-69**.

Regarding claim 62: Baker teaches the either oxycodone or a pharmaceutically acceptable salt can be used in the composition to achieve a synergistic effect, thus demonstrating that these two components (oxycodone and its salts) are functional equivalents. As per MPEP, it further well-known in the art to combine two functional equivalents in order to create a third composition with the same function.

MPEP 2144.06 recites "*It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)."*

The Baker reference further teaches oral administration (reads on the instant oral dosage form of **claim 38**), which can be co-administered in a single dosage form (e.g. see col. 3-8) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially...). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4), which reads on the sustained release formulations of **claim 50**. The Baker et al. reference also teaches that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAIDs such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32). Accordingly, Baker would teach the use of therapeutic and sub-

therapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker reference does not explicitly teach an oral analgesic composition comprising nabumetone instead of ibuprofen. The Baker reference also does not explicitly teach an oral dosage formulation comprising of nabumetone and at least one salt thereof as recited in the instant claims.

However, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; “Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well-established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions”. See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of

the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claims 51** and **66**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutical acceptable salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, thus demonstrating they are functional equivalents.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID nabumetone with the appropriate amount (and/or pharmaceutical acceptable salt thereof) for the NSAID ibuprofen in light of the benefits of nabumetone (increased safety/decreased side effect as compared to ibuprofen) as taught by the Friedel and/or Eversmeyer reference references, to achieve the predictable result of formulating an analgesic oral dosage form for pain treatment. In addition, making and using compounds such as nabumetone and/or pharmaceutical acceptable salt thereof (as part of a combination drug) is routine and known in the art as taught by the cited references.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all cited references have demonstrate the success of making various pharmaceutical formulations comprising various analgesic compounds including oxycodone and nabumetone as well as various pharmaceutical acceptable excipients.

Response to Arguments

Applicant argues that the cited references do not recognize the equivalency of ibuprofen and nabumetone, as there is nothing in the references that suggest a nabumetone-oxycodone combination may result in "unexpectedly enhanced analgesic activity" as disclosed by the Baker reference.

This is not persuasive. There is no requirement in the instant claims that the art teach synergy. Furthermore the motivation to combine the prior art teachings is based on functional equivalency of nabumetone and ibuprofen and absent evidence to the contrary, as these are demonstrated to be functional equivalents, they are expected to produce equivalent synergy.

Applicant argues that nabumetone and ibuprofen are not functional equivalents because they do not have the same selectivity of COX-1 and COX-2 enzymes.

This is not persuasive. As demonstrated above, Friedel and Eversmeyer demonstrate that nabumetone and ibuprofen are functional equivalents. Furthermore, attorney arguments do not take the place of factual evidence and the instant claims do not require the composition to be selective to specific enzymes.

Applicant further argues that the combination of references provide no motivation to modify the composition by substituting ibuprofen with nabumetone, as nabumetone is safer with less side effects and argues that Friedel teaches that side effects were more likely with nabumetone and Eversmeyer teaches that ibuprofen was superior to nabumetone.

This is not persuasive. It is noted that the rejection above has been revised to emphasize that functional equivalency is sufficient motivation to substitute ibuprofen for nabumetone. While the art teaches that different compounds might produce different side effect, this does not take away from their teachings demonstrating functional equivalency, as both are demonstrated by the art to function with equal efficacy as NSAIDs.

Applicants reiterate that the combination of the cited references does not teach or suggest administering nabumetone together with oxycodone, e.g., because the Friedel and Eversmeyer articles describe administration of nabumetone by itself, without any additional analgesic agents. Applicants further submit that there is nothing in the cited references to suggest that administration of nabumetone by itself will not produce adequate analgesia. Accordingly, Applicants submit that the combination of the cited references does not teach or suggest administration of nabumetone in combination with oxycodone as recited in claim 38.

This is not persuasive. Although the references of Friedel and Eversmeyer demonstrate the use of nabumetone by itself, these references are simply cited to teach the pharmacokinetic properties of Nabumetone and demonstrate that nabumetone and ibuprofen are functional equivalents. The primary reference, Baker, is cited to demonstrate the combination of Oxycodone and ibuprofen and as ibuprofen and nabumetone are functional equivalents (both function as NSAIDs) as demonstrated by the teachings of Friedel and Eversmeyer, it would be obvious to one of skill in the art to substitute one for the other, with reasonable expectation of success, absent evidence to the contrary.

Applicant further argues “In response to the Examiner's reliance on the case law on pages 14 and 17 of the Office Action, Applicants respectfully note that the claims at issue in the relied upon cases were not directed to a method of treating pain in a human patient, and that the Examiner's reliance on these cases may therefore be inappropriate.”

This is not persuasive. The case law cited (MPEP 2143.02) states “The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success.” The claims at issue of the case are a demonstration of an example and are not intended to limit the case law to claim pertaining only to methods of treating depressions. As long as the Examiner is able to demonstrate a reasonable expectation of

success, the obviousness rejection is proper. Furthermore, applicant has not demonstrated any factual evidence demonstrating that the reasonable expectation of success presented in the rejection above would not result in a functional composition.

Applicant further argues that the combination of the cited references does not provide a reason for combining nabumetone with a pharmaceutically acceptable excipients "which provides a sustained release of nabumetone" as recited in claim 50, e.g., because the Friedel article describes a mean elimination half-life of, e.g., 38.8 and 26.3 hours, after administration of a single dose of 1 g of nabumetone.

This is not persuasive. Baker teaches sustained release formulations of oxycodone and a NSAID compound, thereby satisfying the limitation of claim 50. Furthermore, applicant hasn't provided any actual evidence demonstrating that the nabumetone of Friedel combined with the Baker reference would not result in a functional sustained release composition.

Applicant further argues that the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, e.g., because the Friedel and Eversmeyer articles describes administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg).

While Friedel and Eversmeyer teach higher ranges of nabumetone, Baker teaches the use of NSAIDs compounds, such as ibuprofen, in amounts ranging from 10-120 mg/kg and 60-300mg, as taught in the above rejection. Based on the teachings of Baker, Friedel and Eversmeyer one of skill in the art is aware that nabumetone and ibuprofen are equally efficacious NSAID compounds, which can be substituted for one another, therefore, nabumetone can be used in the composition of Baker in the quantities taught by Baker to be appropriate for NSAID compounds.

Applicant lastly argues that with respect to secondary considerations, there is no approved product comprising oxycodone and nabumetone currently on the market, more than 26 years after the filing of the Baker patent, which supports applicant position that it was not obvious to modify the compositions of Baker.

This is not persuasive because MPEP does not recognize lack of anticipation to be a secondary consideration.

3. Claims **38**, **47-67** and **70-73** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously) as applied to claims 38, 47, 48, 50-52, 62, 63, 66 and 68-69 above, and further in view of **Oshlack** et al. US Pat. No. 5,472,712 (12/95) or **Oshlack** et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier). The previous rejection over claims 38 and 47-65 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 70-73 is necessitated by applicant's amendment to the claims. (Claims 70-73 recite limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

MPEP 2111.03: For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that

the introduction of additional steps or components would materially change the characteristics of applicant's invention.

For purposes of examination the claims will be interpreted as reciting "comprising" language.

The substance of the above obviousness rejection (the rejection over the combination of Baker, Friedel and Eversmeyer) is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference does not explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or … salt thereof" and "a sustained release of the nabumetone…" as recited in the instant claims 49, 59, 64, 65 etc. The Baker reference also does not explicitly teach using "an immediate release form" for nabumetone in the formulation (as recited in the instant claim 53) as well as formulation comprising particles of 0.5 to 2.5 mm in diameters as recited in the instant claims 57 and 58.

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone, such as utilizing sustained release carriers, beads (or particles with various diameters) as well as using immediate release formulation for non-opioid drugs in a combination drug formulation are known and routine in the art. Using beads/particles coated with the opioid drug including substrate layers which comprise the drugs is also known in the art to produce delayed release of extended duration. For examples, **Oslack** et al ('712 patent) teach drug formulation of sustained (or controlled) release formulation of various compounds including the controlled release of oxycodone (e.g. col.14, lines 15+); Oslack et al ('195 patent) also teach sustained oral formulation for opioid analgesics (e.g. Abstract) including oxycodone (e.g. col.6,

lines 30+). The Oslack ('195) patent specifically teach using particles with diameters of about 0.1mm to about 3 mm (e.g. Abstract), which reads on the particles of **clms 57** and **58**. The Oslack ('195) patent also teaches using "immediate release" formulation for "a second (non-opioid) drug", incorporated into immediate release layer, or coating, etc. (e.g. col.7, lines 21+), which reads on the immediate release formulation of **clm 53** and the coating layer of **clm 59**. The Oslack ('195) reference also teaches incorporating sustained release matrix with the opioid drug (e.g. col.11, lines 30+), which reads on the sustained carrier of **clm 60**. The Oslack ('195) reference also teaches various sustained release carrier such as "hydroxyalkylcellulose" (e.g. col.11, lines 34+), which reads on the sustained carrier of **clm 55**. The Oslack ('195) reference also teaches the sustained release formulations provide about at least 12 hour or about 24 hours, or longer release time for opioid drugs (e.g. col.5, lines 40+), which reads on the release time of **clms 54** and **61**. The Oslack ('195) reference also teaches treating pain for cancer patients (e.g. col.1, lines 50+), which the cancer pain reads on the types of pains listed in **clm 56**. Both of the references also teach the advantages of sustained release formulation. For example, the '195 patent teaches the controlled or sustained release oral dosage formulation would provide effective blood levels of the opioid analgesic for at least about 24 hours (e.g. Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize various known and routine formulations to make various analgesic compositions that have various release rates. For examples, the sustained release carriers for oxycodone including beads/layers as well as the immediate release formulations for the other non-opioid drug in the same formulation as taught by the Oshlack and Oshlack et al. patents. A person of ordinary skill in the art would have been motivated at the time of the invention to use the various formulations as disclosed in Oshlack references (i.e. the various time releasing

formulations) to make a combination drug based on a sustained releasing opioid drug (such as oxycodone) and an immediate releasing non-opioid drug (such as nabumetone), because Baker et al and Oshlack ('195) patent specifically teach "sustained release formulations" for the opioid drug is known and routine, and the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration especially for treatment of cancer pains. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of formulating sustained release formulation (especially for oral administering an opioid analgesic such as oxycodone) as taught by both the Oshlack patent references, to improve the delivery of the analgesic compounds for the predictable result of enabling standard pharmaceutical formulation and administering.

A person of ordinary skill in the art would have been motivated at the time of the invention to use immediate or sustained release formulation for the non-opioid drug (such as Nabumetone) in the same combination drug formulation, because Oshlack ('195) patent teaches the advantages of using immediate release formulation such as an "immediate releasing layer" to coat the opioid drug to afford differential drug release rates for efficient pain treatments. In addition, because all the cited references teach methods of making various combinations of drugs in the same pharmaceutical composition with various releasing matrices, coating, particles, etc., for various pain treatments, it would have been obvious to one skilled in the art to substitute one type of releasing formulation (such as sustained release) for the other (such as immediate release or combinations of sustained and immediate release formulations) to achieve the predictable result of making pharmaceutical composition with optimized drug releasing rates.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of

making and using various drug formulations (including sustained/immediate release formulations, coating, tablets, particle matrix, etc.) especially for various analgesic compounds.

Response to Arguments

Applicants argue that the combination of the cited references does not teach or suggest administering nabumetone together with oxycodone, e.g., because the Friedel and Eversmeyer articles describe administration of nabumetone by itself, without any additional analgesic agents. Applicants further submit that there is nothing in the cited references to suggest that administration of nabumetone by itself will not produce adequate analgesia. Accordingly, Applicants submit that the combination of the cited references does not teach or suggest administration of nabumetone in combination with oxycodone as recited in claim 38.

This is not persuasive. Although the references of Friedel and Eversmeyer demonstrate the use of nabumetone by itself, these references are simply cited to teach the pharmacokinetic properties of Nabumetone and demonstrate that nabumetone and ibuprofen are functional equivalents. The primary reference, Baker, is cited to demonstrate the combination of Oxycodone and ibuprofen and as ibuprofen and nabumetone are functional equivalents (both function as NSAIDs) as demonstrated by the teachings of Friedel and Eversmeyer, it would be obvious to one of skill in the art to substitute one for the other, with reasonable expectation of success, absent evidence to the contrary.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER BERRIOS whose telephone number is (571)270-7679. The examiner can normally be reached on Monday-Thursday: 7:00am-4:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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